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WO 01/58956 A3

(54) Title: ANTIBODIES THAT BIND HUMAN INTERLEUKIN-18 AND METHODS OF MAKING AND USING

(57) Abstract: Antibodies that bind human interleukin-18 (hIL-18) are provided, in particular antibodies that bind epitope(s) of human IL-18. The antibodies can be, for example, entirely human antibodies, recombinant antibodies, or monoclonal antibodies. Preferred antibodies have high affinity for hIL-18 and neutralize hIL-18 activity*in vitro* and *in vivo*. An antibody of the invention can be a full-length antibody or an antigen-binding portion thereof. Method of making and method of using the antibodies of the invention are also provided. The antibodies, or antibody portions, of the invention are useful for detecting hIL-18 and for inhibiting hIL-18 activity, e.g., in a human subject suffering from a disorder in which hIL-18 activity is detrimental.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07K16/24 A61K39/395 C12N5/10 C12N15/13 A61K38/17
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B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07K A61K C12N A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BIOSIS, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 974 600 A (HAYASHIBARA BIOCHEM LAB) 26 January 2000 (2000-01-26) paragraph [0021] paragraph [0038] - paragraph [0040] paragraph [0045] - paragraph [0071] claims 1-27 ---	1-3,53, 55,57,59
X	KOHKA HIDEO ET AL: "Involvement of interleukin-18 (IL-18) in mixed lymphocyte reactions (MLR)." JOURNAL OF INTERFERON AND CYTOKINE RESEARCH, vol. 19, no. 9, 1999, pages 1053-1057, XP001007317 ISSN: 1079-9907 the whole document --- -/--	1,2,53, 55,57, 59,60

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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Date of the actual completion of the international search	Date of mailing of the international search report
24 July 2001	17.09.01

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Renggli, J

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INTERNATIONAL SEARCH REPORT

International Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61P13/00 A61P15/00 A61P17/00 A61P19/00 A61P21/00
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A61P37/00 A61K31/56 A61K31/56 A61K31/56

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 00 56771 A (HOLMES STEPHEN D ;SMITHKLINE BEECHAM PLC (GB); ABDEL MEGUID SHERIN) 28 September 2000 (2000-09-28) page 2 -page 3; claims 1-23	1,2,53, 55,57,59

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Authorized officer
Renggli, J

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 01/04170

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IPC 7 //(A61K39/395,31:505),(A61K39/395,38:13),(A61K39/395,31:445),(A61K39/395,31:56),(A61K39/395,38:17)

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 01/04170

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 53, 55, 57, 59 and 60 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-3,53,55,57,59 (part) and 60

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-3, 53, 55, 57, 59 (part) and 60

A compound capable of binding a human IL-18 amino acid sequence or portion thereof, wherein said amino acid comprises a sequence selected for the group consisting of SEQ ID NO:67 and SEQ ID NO:68 and methods of inhibiting or treating involving the use of said compound.

2. Claims: 4-10, 39-46 (part), 54 (part), 56 (part), 58 (part) and 59 (part)

A human monoclonal antibody, or antigen binding portion thereof, capable of binding to human IL-18 and isolated nucleic acid encoding an CDR of said antibody, host cells containing the said nucleic acid, method of synthesizing said antibody, pharmaceutical compositions comprising said antibody, methods for inhibiting or treating involving the use of said antibody.

3. Claims: 11-15, 39-46 (part), 54 (part), 56 (part), 58 (part) and 59 (part)

An isolated antibody, or an antigen-binding portion thereof, that binds an epitope of human IL-18, or portion thereof, comprising an amino acid sequence selected from the group comprising seq ID:3 and 33 and isolated nucleic acid encoding an CDR of said antibody, host cells containing the said nucleic acid, method of synthesizing said antibody, pharmaceutical compositions comprising said antibody, methods for inhibiting or treating involving the use of said antibody.

4. Claims: 16-21, 39-46 (part), 54 (part), 56 (part), 58 (part) and 59 (part)

An isolated antibody, or antigen-binding portion thereof, that binds to an epitope of human IL-18, wherein the antibody, or antigen-binding portion thereof, dissociates from human IL-18 with a koff rate constant of 0.1 s-1 or less, as determined by surface plasmon resonance, or which inhibits human IL-18 activity with an IC50 of 1 x 10-6 M or less and isolated nucleic acid encoding an CDR of said antibody, host cells containing the said nucleic acid, method of synthesizing said antibody, pharmaceutical compositions comprising said antibody, methods for inhibiting or treating involving the use of said antibody.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

5. Claims: 22-28, 32-35, 39-46 (part), 54 (part), 56 (part), 58 (part) and 59 (part)

An isolated human antibody, or an antigen-binding portion thereof, comprising at least one variable region CDR domain capable of binding an epitope of human IL-18 and isolated nucleic acid encoding an CDR of said antibody, host cells containing the said nucleic acid, method of synthesizing said antibody, pharmaceutical compositions comprising said antibody, methods for inhibiting or treating involving the use of said antibody.

6. Claims: 29-31, 39-46 (part), 54 (part), 56 (part), 58 (part) and 59 (part)

An isolated antibody, or an antigen-binding portion thereof, with a variable region comprising an amino acid sequence selected from the group consisting of seq IDs: 15, 16 and 17 and isolated nucleic acid encoding an CDR of said antibody, host cells containing the said nucleic acid, method of synthesizing said antibody, pharmaceutical compositions comprising said antibody, methods for inhibiting or treating involving the use of said antibody.

7. Claims: 36-38, 39-46 (part), 54 (part), 56 (part), 58 (part) and 59 (part)

An isolated antibody, or an antigen-binding portion thereof, with a variable region comprising an amino acid selected from the group consisting of seq IDs: 26, 27 and 29 and isolated nucleic acid encoding an CDR of said antibody, host cells containing the said nucleic acid, method of synthesizing said antibody, pharmaceutical compositions comprising said antibody, methods for inhibiting or treating involving the use of said antibody.

8. Claims: 47-52

A method of making an antibody that binds human interleukin-18 comprising exposing an antibody repertoire to an antigen comprising an epitope of human IL-18 or portion thereof and selecting from the antibody repertoire an antibody that binds the epitope of human IL-18, or potion thereof.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 01/04170

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0974600 A	26-01-2000	JP 2000236884 A	05-09-2000
WO 0056771 A	28-09-2000	NONE	